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		Project No. Incontinence
TITLE TDS for the treatment of incontinence, part III: Delivery of SPM8224, the free base of Fesoterodine CONFIDENTIAL	Page 1	of 9
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1. SUMMARY

The report describes in vitro skin permeation characteristics of transdermal delivery systems (TDS) containing SPM8224, the free base of Fesoterodine. Test samples were prepared by either lab-scale solvent coating or hot-melt processing. Patches were tested by means of flux rates across hairless mouse skin, selected samples were also investigated in the LACDR human skin model.

High flux rates of SPM8224 across mouse skin were obtained for all batches. The highest initial flux was achieved with a silicone based hot melt formulation.

Permeation across human skin demonstrated the promising potential of SPM8224, the free base of Fesoterodine, for the treatment of overactive bladder. Based on these in vitro data patches with sizes in the range of 15 to 30 cm² could theoretically delivery 4 to 8 mg/24 h which is the current range of the oral Fesoterodine formulation. The data have to be confirmed in vivo.

Besides this, new acrylic based hot melt adhesive from National Starch & Chemical were evaluated. One very promising fomulation could be identified. Provided that other success criteria, such as physico-chemical compatibility with the hot melt process and with different drugs, are met these formulations might fill the gap in hot melt pressure sensitive adhesives for transdermal systems.

Distribution: Original PH DOK F&T, PHA, TS, TT, PH REG, IPM (AS) Summary only/PCD, PH TOX, BA, MOBI, SIL, ILF			
Key words: Fesoterodine, SPM8224, skin permeation in vitro, mouse skin, human skin, hot melt acrylics			
Author	Name	Signature	Date
Head of TS	Dr. A. Breitenbach	<i>A. Breitenbach</i>	
Reviewed by			
Head of TT	Dr. H.-M. Wolff	<i>H.-M. Wolff</i>	
Approved by			
Head of F&T	M.C.F. Hannay	<i>M.C.F. Hannay</i>	

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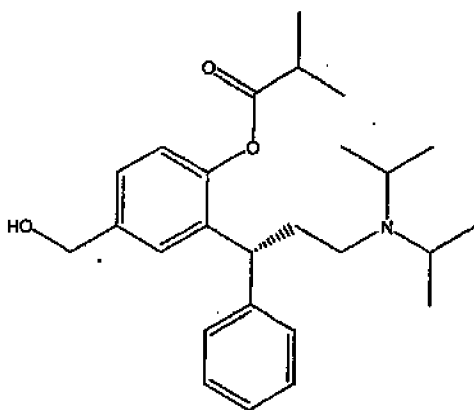
APPENDIX A (Certificates of analysis)

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2. INTRODUCTION AND OBJECTIVES

The objective of the study was to investigate the feasibility of transdermal delivery of SPM8224, the free base of Fesoterodine (scheme 1).



Scheme 1: Chemical structure of the free base of Fesoterodine

Therefore, several lab scale patch batches containing SPM8224 were prepared and investigated by means of in vitro drug permeation across hairless mouse skin. Subsequently, selected samples were investigated in a human skin model, as well.

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3. MATERIALS AND METHODS

For a detailed description of the experiments refer to the batch documentation.

Hot-melt patches (exemplary): 8 g of a preformed silicone adhesive were weighed into a beaker and tempered at 160°C for ca. 20 min to achieve a homogenous melt. 0.5 g of inner phase polymer (e.g. poly(ethylene oxide) and 1.5 g of drug were added. After tempering at 160°C for additional 5 min the mixture was homogenized manually and further processed on the pre-tempered Chill-Roll (120°C, 250 µm) for lamination.

5 cm² patches were isolated by manual punching followed by determination of the average patch weight (n=10). Finally, patches were sealed individually in pouches.

Mouse Skin Model (PHA): according to OBU0469.ABV100, rev. 00 (1998) with an active diffusion area of 2.55 cm², a phosphate buffer acceptor phase at pH 6.2 and a temperature of 32°C, n=3

Human Skin Model (LACDR):

according to H. Tanojo et al. , J. Control Rel. 45 (1997) 41-47.

skin from abdomen with a thickness of approx. 250 µm, flux experiment: acceptor phase: PBS, pH= 6.2, temperature: 32°C, diffusion cells with spiral groove (8 cells), groove area: 0.552 cm², dialysis membrane used as separator between skin and acceptor phase
flux: 5 ml/hour PBS, experiment runs for 72 hours, sampling cycle: 3 hours

Analytical Methods (PHA): refer to certificates of analysis

Data Analysis: sigmoidal Boltzmann and linear fit: Microcal Origin 6.0

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4. RESULTS AND DISCUSSION

The free base of Fesoterodine is an oily substance and was used with a purity of approx. 90%. Several lab scale patch batches with different compositions were prepared by either solvent coating or hot melt processing and the preparation presented no difficulties. The properties of these batches are summarized in table 1.

Table 1: Properties of the patch batches

No	Lot No. (Ch.B.)	PSA	Theo. drug loading [% (w/w)]	Patch weight (n=10) [g/m ²]
1	20111080	SC acrylic	15	100
2	20111085	HM EVA	15	84
3	20111086	HM silicone	15	63
4	20111087	HM SxS	15	89
5	20111095	HM acrylic 01	15	73
6	20201027	HM acrylic 02	15	121
7	20201028	HM acrylic 03	15	115

SC Acrylic = solvent coating, acrylic type adhesive, Duro Tak 387-2287, National Starch & Chemical (NSC)
 HM EVA = hot melt, ethylene vinyl acetate co-polymer adhesive, Dispoifix 213, NSC
 HM Silicone = hot melt silicone based adhesive, BioPSA + 5% (w/w) Ozokerite wax, DowCorning
 HM SxS = hot melt, styrene block co-polymer, in house formulation
 HM Acrylic 0x = hot melt acrylic type adhesives, experimental formulations from NSC, refer to Annex

All batches were tested in the hairless mouse skin model.

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Fig. 1 outlines the cumulative permeation of SPM8224 across hairless mouse skin (HMS) from patches prepared with the most common adhesive classes, acrylic based, ethylene vinyl acetate based (EVA), silicone based and poly(styrene) based (SxS). The flux rates were expressed as permeation of active metabolite, which is the hydrolysis di-hydroxy product (SPM7605).

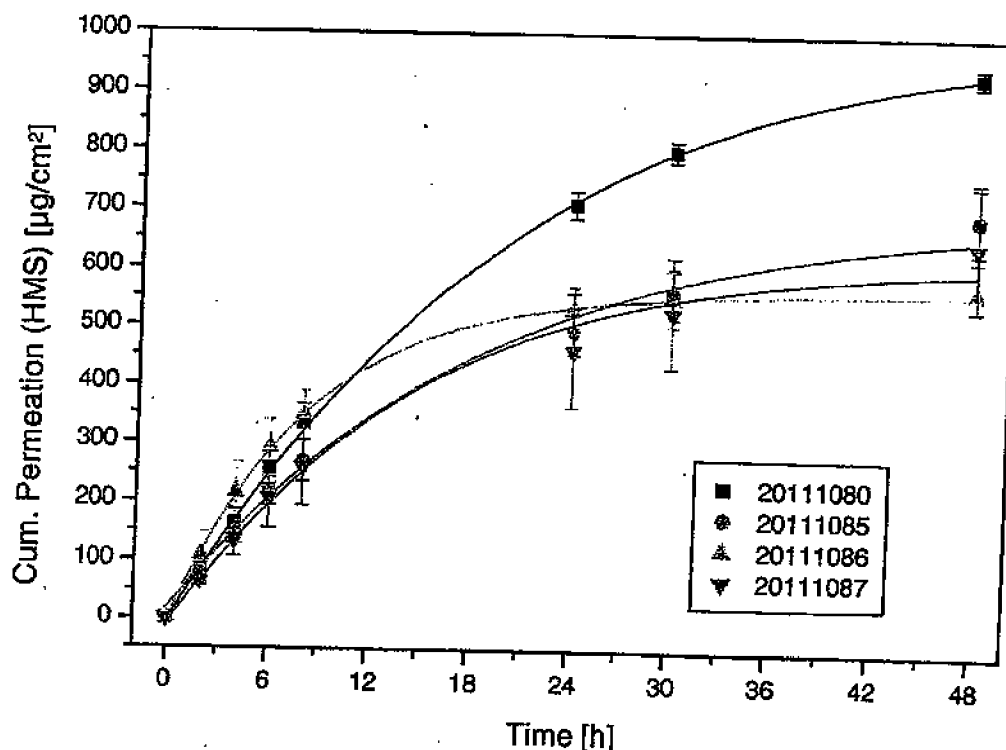


Fig. 1: Cumulative drug permeation (calculated as permeation of active metabolite, SPM7605)

In all cases high flux rates were observed following a non-linear release kinetics. The flux rates from EVA and SxS matrices were nearly identical. Higher initial rates were obtained for the silicone and the acrylic based systems. While the silicone type batch showed the highest drug permeation in the first 6 to 8 h, the subsequent higher values for the acrylic based patch were mainly due to a higher patch weight.

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Fig. 2 illustrates the drug permeation across hairless mouse skin (HMS) from new types of pressure sensitive adhesives (PSA): for the first time it was possible to test the performance of acrylic based patch batches which were prepared by hot melt processing. The three different experimental PSA were exclusively obtained from National Starch & Chemical.

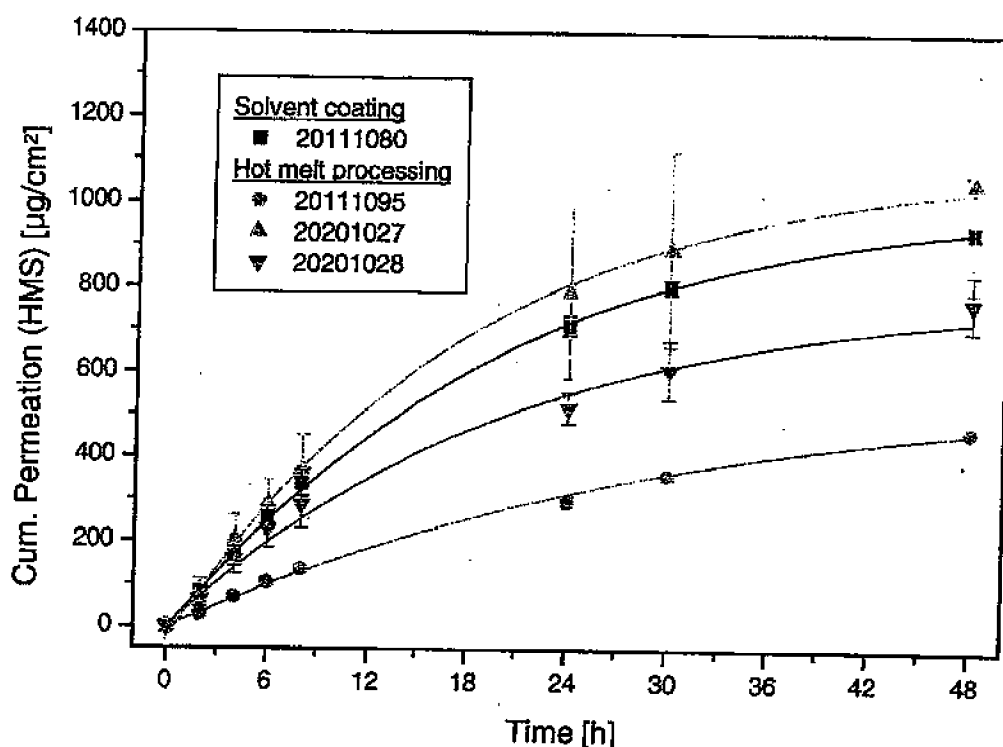


Fig. 2: Cumulative drug permeation (calculated as permeation of active metabolite, SPM7605)

While two of these new PSA (batches 20111095 and 20201028) yielded lower flux rates, it was possible with the third PSA (batch 20201027) to achieve flux rates comparable to the solvent born system (batch 20111080). Although still in an experimental stage this new class of acrylic based PSA seems to be capable of closing the final gap in hot melt processing, since up to now the use of acrylics was limited to solvent coating, only.

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Two batches were investigated in the LACDR human skin model. Since the skin supporting silicone membrane in this model was hindering drug flux it was exchanged with a dialysis membrane. Fig. 3 demonstrates the obtained flux rates across the composite of excised human skin supported with a dialysis membrane (EHS/DM).

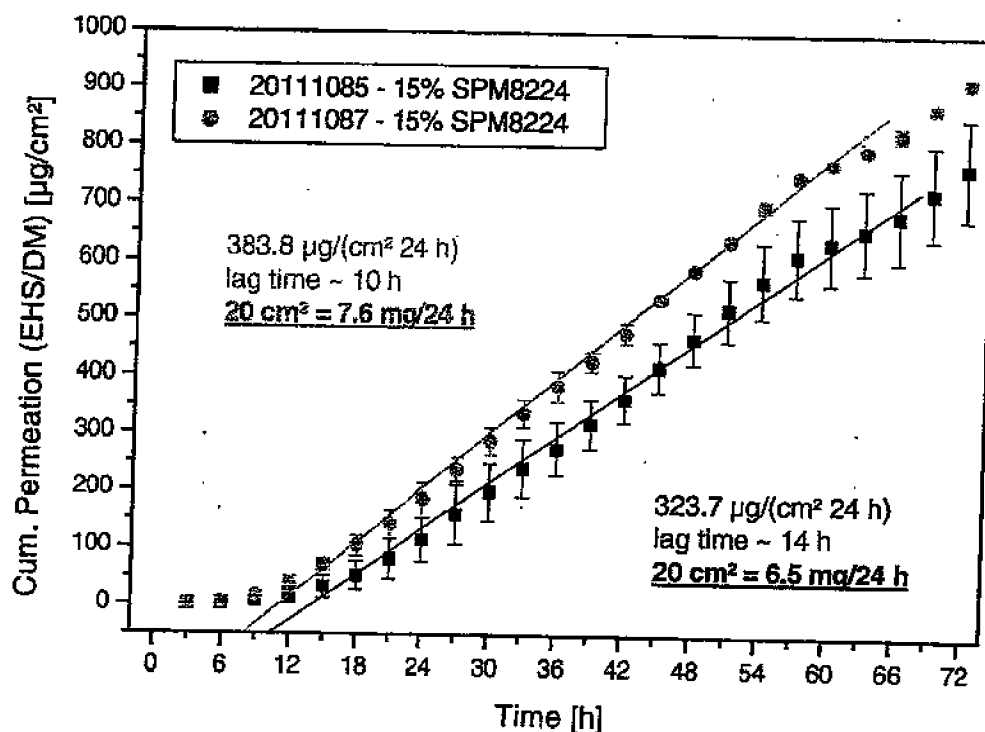


Fig. 3: Cumulative drug permeation (calculated as permeation of active metabolite, SPM7605)

After short lag-times of 6 to 8 h (which are not predictive for the in vivo situation) both batches showed a high steady state flux for at least 2.5 d. From these results patches with a size of already 20 cm^2 could theoretically deliver therapeutic doses of the free base of Fesoterodine, compared to the oral formulation.

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CONCLUSIONS

Several lab scale patch batches containing the free base of Fesoterodine were prepared and tested by means of in vitro drug permeation across mouse skin and human skin.

Based on the results obtained, the flux rates were found to be sufficient for the treatment of overactive bladder with patch sizes in the range of 15 to 30 cm² (equal to ca. 4 to 8 mg/24 h).

Moreover, in cooperation with National Starch & Chemical a new series of hot melt acrylics could be developed. These new adhesives could close an actual gap in hot melt pressure sensitive adhesive (PSA) formulation for transdermal systems. To further evaluate this class of PSA an investigation on physico-chemical compatibility with the hot melt process and different drug substances has to be performed.

ANNEX 1

Copies of the Certificates of Analysis

(signed originals stored at PH DOK)

Analysenzertifikat in vitro Freisetzung durch Mäusehaut

Präparat : SPM 907 Ch.-B.: 20111080
 Wirkstoff : **SPM 8224**
 Sollgehalt : 15 % TDS - Fläche: 5 cm²
 ABV vom : analog OB 0469.ABV.100 Analysendatum :

Ausgangsanalyse

Bemerkungen: Puffer pH 6,2 KT Freisetzungsfläche 2,55 cm²
 Mäusehautdicke: 1=161 µm; 2=168 µm, 3=172 µm, 34,5g
 Alter lebend: 8 Wochen, TK-Schrank 10 Wochen SKH-1 ♂
HPLC-Bedingungen:
 Eluent: 600 VT Wasser : 400 VT ACN : 1 VT Trifluoressigsäure
 Temperatur: 35°
 Wellenlänge: 220 nm
 Fluss: 1 ml
 Säule: Waters Spherisorb Nitrile 5µm

Tabelle der kumulierten Freisetzung in µg SPM 8224/1 cm²

Zeit [h]	1	2	3	MW	SD
2	55,67	84,70	72,02	70,80	14,6
4	122,20	170,16	138,78	143,71	24,4
6	198,00	256,39	218,78	224,39	29,6
8	263,98	330,41	286,25	293,55	33,8
24	501,55	599,45	570,07	557,02	50,2
30	572,00	664,50	646,75	627,75	49,1
48	653,61	738,79	750,20	714,20	52,8

MW = Mittelwert SD = Standardabweichung

Achsenabschnitt (b) = 74,6 µg
 Regressionskoeffizient (m) = 20,83 µg/h
 Korrelationskoeffizient (r) = 0,9786 3-24h

Tabelle der kumulierten Freisetzung in µg SPM 7605/1 cm²

Zeit[h]	1	2	3	MW	SD
2	21,74	23,83	19,57	21,71	2,1
4	44,25	48,65	42,13	45,01	3,3
6	69,47	73,58	67,88	70,31	2,9
8	91,83	96,11	88,95	92,30	3,6
24	277,04	239,90	228,10	248,35	25,5
30	312,79	269,83	261,67	281,43	27,5
48	377,09	322,27	327,26	342,21	30,3

MW = Mittelwert SD = Standardabweichung

Achsenabschnitt (b) = 6,0 µg
 Regressionskoeffizient (m) = 10,17 µg/h
 Korrelationskoeffizient (r) = 0,9990 3-24h

Datum

Fabert (PHA)

Dr. Seiffert (PHA)

Analysenzertifikat in vitro Freisetzung durch Mäusehaut

Präparat : SPM 907 Ch.-B.: 20111085
 Wirkstoff : **SPM 8224**
 Sollgehalt : 15 % TDS - Fläche: 5 cm²
 ABV vom : analog OB 0469.ABV.100 Analysendatum :

Ausgangsanalyse

Bemerkungen: Puffer pH 6,2 KT Freisetzungsfläche 2,55 cm²
 Mäusehautdicke: 1=174 µm; 2=159µm, 3=190µm, 35,5g
 Alter lebend: 8 Wochen, TK-Schrank 10 Wochen SKH-1 ♂
HPLC-Bedingungen:
 Eluent: 600 VT Wasser: 400 VT ACN: 1 VT Trifluoressigsäure
 Temperatur: 35°
 Wellenlänge: 220 nm
 Fluss: 1 ml
 Säule: Waters Spherisorb Nitrile 5µm

Tabelle der kumulierten Freisetzung in µg SPM 8224/1 cm²

Zeit [h]	1	2	3	MW	SD
2	58,74	72,97	104,26	78,66	23,3
4	121,08	130,31	162,74	138,04	21,9
6	188,37	183,76	239,35	203,82	30,8
8	238,21	223,26	286,98	249,48	33,3
24	410,84	379,08	463,27	417,73	42,5
30	470,84	428,55	518,49	472,63	45,0
48	572,15	507,03	629,89	569,69	61,5

MW = Mittelwert SD = Standardabweichung

Achsenabschnitt (b) = 92,7 µg
 Regressionskoeffizient (m) = 14,19 µg/h
 Korrelationskoeffizient (r) = 0,9641 3-24h

Tabelle der kumulierten Freisetzung in µg SPM 7605/1 cm²

Zeit[h]	1	2	3	MW	SD
2	14,65	18,20	20,52	17,79	3,0
4	32,93	34,65	34,64	34,07	1,0
6	52,29	50,29	53,65	52,07	1,7
8	67,36	52,25	66,03	61,88	8,4
24	163,98	136,16	146,39	148,84	14,1
30	187,17	156,71	164,01	169,30	15,9
48	246,26	207,59	207,87	220,57	22,2

MW = Mittelwert SD = Standardabweichung

Achsenabschnitt (b) = 12,1 µg
 Regressionskoeffizient (m) = 5,77 µg/h
 Korrelationskoeffizient (r) = 0,9961 3-24h

Datum

Fabert (PHA)

Dr. Seiffert (PHA)

Analysenzertifikat in vitro Freisetzung durch Mäusehaut

Präparat :	SPM 907 TDS	Ch.-B.:	20111086
Wirkstoff :	SPM 8224		
Sollgehalt :	15%	TDS - Fläche:	5 cm²
ABV vorn :	analog OB 0469.ABV.100	Analysendatum :	

Ausgangsanalyse

Bemerkungen: Puffer pH 6,2 KT Freisetzungsfläche 2,55 cm²
Mäusehautdicke: 1=188 µm; 2=172µm, 3=167µm, 32,7g
Alter lebend: 9 Wochen, TK-Schrank 7 Wochen SKH-1 ♂
HPLC-Bedingungen:
Eluent: 600 VT Wasser ; 400 VT ACN : 1 VT Trifluoressigsäure
Temperatur: 35°
Wellenlänge: 220 nm
Fluss: 1 ml
Säule: Waters Spherisorb Nitrile 5µm

Tabelle der kumulierten Freisetzung in $\mu\text{g SPM}_{10}/1 \text{ cm}^2$

Zeit [h]	1	2	3	MW	SD
2	151,6	86,7	72,8	103,7	42,0
4	264,1	194,6	165,7	208,1	50,6
6	329,6	274,1	234,0	279,2	48,0
8	370,9	340,3	291,7	334,3	39,9
24	438,3	538,7	479,3	485,5	50,5
30	442,8	556,4	503,5	500,9	56,8
48	444,3	563,8	521,3	509,8	60,6

MW = Mittelwert SD = Standardabweichung

MW = Mittelwert SD = Standardabweichung

Achsenabschnitt (b)=	150,3	µg
Regressionskoeffizient (m) =	14,98	µg/h
Korrelationskoeffizient (r) =	0,9227	3-24h

Tabelle der kumulierten Freisetzung in $\mu\text{g SPM}_{7605/1} \text{ cm}^{-2}$

Zeit[h]	1	2	3	MW	SD
2	28,0	18,2	18,3	21,5	5,6
4	52,4	37,3	38,3	42,7	8,5
6	69,4	51,7	53,3	58,1	9,8
8	82,4	64,3	66,5	71,1	9,8
24	127,3	122,2	138,2	129,2	8,1
30	131,6	130,6	149,8	137,3	10,8
48	135,5	138,8	162,2	145,5	14,6

MW = Mittelwert SD = Standardabweichung

MW = Mittelwert SD = Standardabweichung

Achsenabschnitt (b)=	24,8	µg
Regressionskoeffizient (m) =	4,51	µg/h
Korrelationskoeffizient (r) =	0,9763	3-24h

Analysenzertifikat in vitro Freisetzung durch Mäusehaut

Präparat : SPM 907 Ch.-B.: 20111087
 Wirkstoff : **SPM 8224**
 Sollgehalt : 15 % TDS - Fläche: 5 cm²
 ABV vom : analog OB 0469.ABV.100 Analysendatum : 03.11.2011

Ausgangsanalyse

Bemerkungen: Puffer pH 6,2 KT Freisetzungsfläche 2,55 cm²
 Mäusehautdicke: 1=170 µm; 2=162 µm, 3=160 µm, 31,3g
 Alter lebend: 8 Wochen, TK-Schrank 10 Wochen SKH-1 ♂
HPLC-Bedingungen:
 Eluent: 600 VT Wasser ; 400 VT ACN : 1 VT Trifluoressigsäure
 Temperatur: 35°
 Wellenlänge: 220 nm
 Fluss: 1 ml
 Säule: Waters Spherisorb Nitrile 5µm

Tabelle der kumulierten Freisetzung in µg SPM 8224/1·cm²

Zeit [h]	1	2	3	MW	SD
2	44,72	59,11	64,84	56,22	10,4
4	85,65	140,79	132,93	119,79	29,8
6	121,63	218,35	205,37	181,78	52,5
8	150,10	269,83	254,75	224,89	65,2
24	257,35	417,04	435,07	369,82	97,8
30	317,34	466,51	490,29	424,71	93,7
48	384,12	541,07	603,89	509,69	113,2

MW = Mittelwert SD = Standardabweichung

Achsenabschnitt (b) = 77,2 µg
 Regressionskoeffizient (m) = 12,87 µg/h
 Korrelationskoeffizient (r) = 0,9521 3-24h

Tabelle der kumulierten Freisetzung in µg SPM 7605/1 cm²

Zeit[h]	1	2	3	MW	SD
2	17,57	20,90	16,42	18,30	2,3
4	33,57	45,48	32,25	37,10	7,3
6	49,28	70,25	50,44	56,66	11,8
8	62,80	89,55	64,09	72,15	15,1
24	137,51	190,84	138,64	155,66	30,5
30	157,04	214,82	156,88	176,25	33,4
48	204,06	268,98	203,75	225,60	37,6

MW = Mittelwert SD = Standardabweichung

Achsenabschnitt (b) = 15,3 µg
 Regressionskoeffizient (m) = 5,98 µg/h
 Korrelationskoeffizient (r) = 0,9908 3-24h

Datum

Fabert (PHA)

Dr.Seiffert (PHA)

Analysezertifikat in vitro Freisetzung durch Mäusehaut

Präparat :	SPM 907 TDS	Ch.-B.:	20111095
Wirkstoff :	SPM 8224		
Sollgehalt :	15%	TDS - Fläche:	5 cm ²
ABV vom :	analog OB 0469.ABV.100	Analysendatum :	

Ausgangsanalyse

Bemerkungen: Puffer pH 6,2 KT Freisetzungsfläche 2,55 cm²
Mäusehautdicke: 1=182 µm; 2=169 µm, 3=176 µm, 32,9 g
Alter lebend: 9 Wochen, TK-Schrank 7 Wochen SKH-1 ♂
HPLC-Bedingungen:
Eluent: 600 VT Wasser : 400 VT ACN : 1 VT Trifluoressigsäure
Temperatur: 35°
Wellenlänge: 220 nm
Fluss: 1 ml
Säule: Waters Spherisorb Nitrile 5µm

Tabelle der kumulierten Freisetzung in µg SPM 8224/1 cm²

Zeit [h]	1	2	3	MW	SD
2	25,7	18,1	21,6	21,8	3,8
4	59,7	47,3	51,8	52,9	6,3
6	87,4	69,2	77,4	78,0	9,1
8	110,2	94,2	100,3	101,6	8,1
24	199,6	212,8	211,4	207,9	7,3
30	253,2	245,3	245,5	248,0	4,5
48	322,0	313,3	318,8	318,1	4,4

MW = Mittelwert SD = Standardabweichung

Achsenabschnitt (b)=	22,4	µg
Regressionskoeffizient (m) =	7,96	µg/h
Korrelationskoeffizient (r) =	0,9849	3-24h

Tabelle der kumulierten Freisetzung in µg SPM 7605/1 cm²

Zeit[h]	1	2	3	MW	SD
2	11,9	10,9	10,7	11,2	0,6
4	26,9	26,7	24,3	26,0	1,4
6	40,0	38,9	35,6	38,2	2,3
8	51,3	52,1	45,7	49,7	3,5
24	112,7	131,2	121,5	121,8	9,3
30	151,7	155,3	140,9	149,3	7,5
48	198,4	210,1	189,2	199,2	10,5

MW = Mittelwert SD = Standardabweichung

Achsenabschnitt (b)=	6,5	µg
Regressionskoeffizient (m) =	4,87	µg/h
Korrelationskoeffizient (r) =	0,9965	3-24h

Analysenzertifikat in vitro Freisetzung durch Mäusehaut

Präparat :	SPM 907 TDS	Ch.-B.:	20201027
Wirkstoff :	SPM 8224		
Sollgehalt :	15%	TDS - Fläche:	5 cm ²
ABV vom :	analog OB 0469.ABV.100	Analysendatum :	

Ausgangsanalyse

Bemerkungen: Puffer pH 6,2 KT Freisetzungsfläche 2,55 cm²
Mäusehautdicke: 1=150 µm; 2=148 µm, 3=158 µm, 29,4g
Alter lebend: 8 Wochen, TK-Schrank 12 Wochen SKH-1 ♂
HPLC-Bedingungen:
Eluent: 600 VT Wasser : 400 VT ACN : 1 VT Trifluoressigsäure
Temperatur: 35°
Wellenlänge: 220 nm
Fluss: 1 ml
Säule: Waters Spherisorb Nitrile 5µm

Tabelle der kumulierten Freisetzung in µg SPM 8224/1 cm²

Zeit [h]	1	2	3	MW	SD
2	51,3	109,4	80,4	80,4	29,0
4	129,0	217,5	232,3	192,9	55,9
6	208,8	300,8	308,0	272,5	55,3
8	261,7	364,5	422,5	349,6	81,5
24	549,2	591,4	966,0	702,2	229,4
30	634,2	633,6	1081,0	782,9	258,1
48	801,5	680,0	1236,8	906,1	292,8

MW = Mittelwert SD = Standardabweichung

Achsenabschnitt (b)=	87,0	µg
Regressionskoeffizient (m) =	26,42	µg/h
Korrelationskoeffizient (r) =	0,9836	3-24h

Tabelle der kumulierten Freisetzung in µg SPM 7605/1 cm²

Zeit[h]	1	2	3	MW	SD
2	14,1	20,5	17,3	17,3	3,2
4	32,2	41,9	56,9	43,7	12,5
6	49,3	59,5	73,1	60,6	12,0
8	65,2	77,4	93,1	78,6	14,0
24	180,8	217,9	213,9	204,2	20,3
30	216,1	248,6	256,0	240,2	21,2
48	284,6	290,7	313,5	296,3	15,2

MW = Mittelwert SD = Standardabweichung

Achsenabschnitt (b)=	8,4	µg
Regressionskoeffizient (m) =	8,24	µg/h
Korrelationskoeffizient (r) =	0,9978	3-24h

Datum

Fabert (PHA)

Dr.Seiffert (PHA)

Analysenzertifikat in vitro Freisetzung durch Mäusehaut

Präparat :	SPM 907	Ch.-B.:	20201028
Wirkstoff :	SPM 8224		
Sollgehalt :	15%	TDS - Fläche:	5 cm ²
ABV vom :	analog OB 0469.ABV.100	Analysendatum :	

Ausgangsanalyse

Bemerkungen: Puffer pH 6,2 KT Freisetzungsfläche 2,55 cm²
Mäusehautdicke: 1=158 µm; 2=168µm, 3=171µm, 31,4g
Alter lebend: 8 Wochen, TK-Schrank 12 Wochen SKH-1 ♂
HPLC-Bedingungen:
Eluent: 600 VT Wasser : 400 VT ACN : 1 VT Trifluoressigsäure
Temperatur: 35°
Wellenlänge: 220 nm
Fluss: 1 ml
Säule: Waters Spherisorb Nitrile 5µm

Tabelle der kumulierten Freisetzung in µg SPM 8224/1 cm²

Zeit [h]	1	2	3	MW	SD
2	67,0	46,4	9,0	40,8	29,4
4	166,9	120,0	23,2	103,4	73,3
6	240,8	177,4	33,6	150,6	106,2
8	294,4	217,3	39,8	183,8	130,6
24	314,8	282,5	41,1	212,8	149,6
30	370,7	318,0	43,0	243,9	176,0
48	445,8	418,3	48,1	304,1	222,1

MW = Mittelwert SD = Standardabweichung

Achsenabschnitt (b)=	84,4	µg
Regressionskoeffizient (m) =	6,13	µg/h
Korrelationskoeffizient (r) =	0,7917	3-24h

Tabelle der kumulierten Freisetzung in µg SPM 7605/1 cm²

Zeit[h]	1	2	3	MW	SD
2	18,4	13,9	6,7	13,0	5,9
4	40,8	33,6	15,1	29,9	13,3
6	60,8	51,1	21,3	44,4	20,6
8	80,3	67,0	26,9	58,1	27,8
24	282,3	256,8	86,4	208,5	106,5
30	347,9	294,7	93,9	245,5	134,0
48	444,3	372,3	117,1	311,2	171,9

MW = Mittelwert SD = Standardabweichung

Achsenabschnitt (b)=	-8,1	µg
Regressionskoeffizient (m) =	8,96	µg/h
Korrelationskoeffizient (r) =	0,9990	3-24h

Diffusion experiment with SPM 907 patches on full human skin

Experiment number: 907DF004

Purpose of the study:

To investigate the permeation rate of SPM 907 through skin from two newly formulated patches.

Patch:

Active ingredient: SPM 907

Batch numbers: 20111085 and 20111087

Patch area: 5 cm²

Active ingredient content: 15% SPM 8224

Skin donor:

Birth date: 1964

Sex: female

Skin from: abdomen (belly)

Thickness of dermatomised skin: approximately 250 µm

Diffusion experiment:

Date:

Used cells:

diffusion cells with spiral groove (n=8); groove area: 0.552 cm²

Separator between acceptor phase and skin/patch:

Diachema dialysis membrane, type 10.14, supplied by Dianormi, München, Germany.

Manufactured from neutral cellulose; molar weight cut-off: 5000; thickness (dry): 25 µm.

Pretreated according to the manufacturer's recommendations.

Diameter of separator, skin and patch punch-outs: 1.8 cm.

Setup diffusion cells:

Cell nr.	Cells with/without skin	Batch
1 & 2	with	20111085
3 & 4	with	20111087
5 & 6	without	20111085
7 & 8	without	20111087

Acceptor phase: PBS pH=6.2

Measured temperature waterbath: 32.0 °C

Flux of acceptor phase: 5 ml/hour

Total duration of the experiment: 72 hours, samples are collected in 3 hour periods.

Observations during dermatomisation, cell assembly, disassembly, etc.

Some of the glue from the patch disks destined for cells 7 and 8 remained on the protective foil.

Mass and volume data on the collected fractions

Faktor zur Umrechnung auf cm²=

1,812

measured density of the used acceptor	1,007	g/ml
phase:		

Flux time (hours)	cell nr.	mass tubes (g)	empty	full	volume fractions (ml)	8224 µg/ml	µg/fraction	Fraction F=1.812	Mittelwert	D10H µg/ml	µg/fraction	Fraction x F	Mittelwert
3	1	16,946	33,389		16,329	0,00	0,000	0,000	0,000	0,02	0,327	0,592	
	2	17,037	32,958		15,810	0,00	0,000	0,000	0,000	0,01	0,158	0,286	0,439
	3	17,103	32,928		15,715	0,00	0,000	0,000	0,000	0,02	0,314	0,570	
	4	17,146	32,959		15,703	0,00	0,000	0,000	0,000	0,02	0,314	0,589	0,569
	5	17,010	33,141		16,019	11,90	190,626	345,412	381,152	0,84	13,456	24,382	27,688
	6	17,147	32,666		15,410	14,93	230,073	416,893	550,103	1,51	22,978	41,637	45,936
	7	17,058	32,382		15,217	19,95	303,589	550,103	596,357	1,78	27,723	50,235	55,936
	8	17,132	32,816		15,575	22,77	354,642	642,612	842,612	0,10	1,827	2,947	1,617
6	1	16,652	33,032		16,266	0,01	0,163	0,295	0,285	0,10	0,158	0,287	3,994
	2	16,782	32,711		15,818	0,00	0,000	0,000	0,147	0,01	0,158	0,287	1,617
	3	16,689	32,554		15,755	0,01	0,158	0,285	0,285	0,09	1,418	2,569	3,994
	4	17,020	32,867		15,737	0,01	0,157	0,285	0,285	0,19	2,990	5,418	3,994
	5	17,187	33,320		16,021	8,16	130,730	236,883	201,356	0,80	9,613	17,418	18,077
	6	17,126	32,667		15,433	5,93	91,518	185,830	201,356	0,67	10,340	18,736	18,077
	7	16,897	32,273		15,269	6,88	105,062	190,353	210,737	0,54	8,245	14,941	16,370
	8	17,104	32,806		15,593	8,18	127,550	231,120	210,737	0,53	9,823	17,800	16,370
9	1	17,069	33,458		16,275	0,02	0,326	0,590	0,295	0,22	3,581	6,488	3,959
	2	17,072	32,971		15,788	0,00	0,000	0,000	0,295	0,05	0,789	1,430	3,959
	3	17,137	33,008		15,761	0,03	0,473	0,857	0,988	0,28	4,413	7,996	10,974
	4	17,055	32,888		15,713	0,04	0,629	1,139	0,988	0,49	7,699	13,951	10,974
	5	17,152	33,284		16,020	5,80	92,915	168,362	166,680	0,45	7,209	13,063	12,974
	6	17,095	32,863		15,460	5,88	91,058	164,997	166,680	0,46	7,111	12,886	12,974
	7	17,043	32,447		15,297	6,32	96,677	175,178	172,939	0,50	7,648	13,859	13,006
	8	17,063	32,789		15,597	6,04	94,205	170,699	172,939	0,43	6,707	12,152	13,006
12	1	16,941	33,300		16,245	0,05	0,812	1,472	1,850	0,49	7,960	14,424	9,355
	2	16,877	32,756		15,769	0,01	0,158	0,286	0,879	0,15	2,365	4,286	9,355
	3	17,152	32,980		15,718	0,05	0,786	1,424	1,850	0,44	6,916	12,532	17,501
	4	17,099	32,896		15,697	0,08	1,258	2,275	1,850	0,79	12,401	22,470	17,501
	5	17,086	33,224		16,026	7,03	112,682	204,143	171,324	0,60	9,615	17,423	14,028
	6	16,987	32,537		15,442	4,95	76,437	138,505	171,324	0,38	5,868	10,633	14,028
	7	16,878	32,247		15,262	8,07	123,166	223,176	179,557	0,70	10,684	19,359	15,180
	8	17,293	32,989		15,597	4,81	75,021	135,938	179,557	0,39	6,083	11,022	15,180

15	1	17,050	33,415	16,261	0,08	1,300	2,356	1,750	0,58	9,426	17,079	
	2	17,230	33,132	15,791	0,04	0,632	1,145		0,34	5,369	9,729	13,404
	3	17,236	33,082	15,737	0,17	2,675	4,848		1,20	18,884	34,218	
	4	17,340	33,167	15,717	0,13	2,043	3,702	4,275	1,04	16,346	29,618	31,918
	5	17,254	33,376	16,010	3,66	56,995	103,276		0,30	4,803	8,703	
	6	16,879	32,401	15,414	4,70	72,446	131,273	117,274	0,36	5,649	10,055	9,379
	7	17,091	32,476	15,278	5,02	76,696	138,973		0,43	6,570	11,904	
	8	17,301	33,003	15,593	4,15	64,710	117,255	128,114	0,35	5,457	9,889	10,897
18	1	16,756	33,089	16,219	0,12	1,946	3,527		0,69	11,191	20,279	
	2	16,708	32,561	15,745	0,08	1,260	2,282	2,905	0,51	8,030	14,550	17,414
	3	17,087	32,910	15,733	0,16	2,517	4,561		0,84	13,216	23,947	
	4	16,644	32,417	15,663	0,19	2,978	5,393	4,977	1,20	18,796	34,058	29,003
	5	17,139	33,226	15,975	3,94	62,942	114,051		0,31	4,952	8,974	
	6	16,988	32,533	15,437	4,28	66,070	119,719	116,885	0,36	5,557	10,070	9,522
	7	16,756	32,129	15,266	4,02	61,370	111,202		0,35	5,343	9,682	
	8	17,198	32,872	15,565	3,65	56,812	102,944	107,073	0,34	5,292	9,589	9,636
21	1	17,056	33,287	16,118	0,21	3,385	6,133		1,08	17,408	31,543	
	2	17,178	32,924	15,637	0,13	2,033	3,683	4,908	0,69	10,789	19,550	25,546
	3	17,124	32,859	15,626	0,22	3,438	6,229		1,02	15,938	28,880	
	4	16,860	32,564	15,595	0,25	3,899	7,064	6,647	1,31	20,429	37,018	32,949
	5	17,110	33,120	15,899	3,60	57,235	103,710		0,35	5,565	10,083	
	6	17,040	32,454	15,307	3,57	54,845	99,018	101,364	0,35	5,357	9,708	9,895
	7	17,224	32,489	15,159	3,12	47,296	85,700		0,33	5,002	9,064	
	8	17,244	32,821	15,469	3,32	51,356	93,057	89,379	0,34	5,259	9,530	9,297
24	1	17,187	33,397	16,087	0,24	3,863	7,000		1,03	16,580	30,043	
	2	17,224	32,953	15,620	0,20	3,124	5,661	6,330	0,92	14,370	26,039	28,041
	3	17,135	32,842	15,598	0,29	4,523	8,196		1,17	18,249	33,068	
	4	17,061	32,729	15,559	0,31	4,823	8,740	8,468	1,40	21,783	39,470	36,269
	5	17,198	33,183	15,874	2,90	46,034	83,414		0,28	4,446	8,054	
	6	17,100	32,514	15,307	3,29	50,360	91,251	87,333	0,33	5,051	9,153	8,603
	7	16,888	32,244	15,150	2,83	42,374	77,688		0,31	4,696	8,510	
	8	17,085	32,657	15,464	2,81	43,453	78,737	78,213	0,29	4,484	8,126	8,318
27	1	16,864	33,063	16,086	0,40	6,435	11,659		1,54	24,773	44,889	
	2	17,205	32,938	15,624	0,25	3,806	7,078	9,368	1,03	16,092	29,159	37,024
	3	16,647	32,340	15,584	0,45	7,013	12,707		1,67	26,025	47,158	
	4	17,273	32,939	15,557	0,34	5,289	9,584	11,146	1,40	21,780	39,465	43,311
	5	17,220	33,197	15,866	3,23	51,247	92,860		0,32	5,077	9,200	
	6	17,038	32,460	15,315	2,54	38,900	70,486	81,673	0,25	3,829	8,938	8,069
	7	17,177	32,434	15,151	3,13	47,422	85,929		0,35	5,303	9,609	
	8	17,055	32,818	15,455	2,31	35,701	64,690	75,310	0,23	3,555	6,441	8,025

30	1	17,290	33,506	16,103	0.31	4,992	9,046	8,907	1.09	17,553	31,805	32,450
	2	16,867	32,587	15,611	0.31	4,839	8,769		1.17	18,265	33,095	
	3	17,150	32,855	15,598	0.42	6,550	11,869		1.34	20,898	37,868	
	4	16,463	32,138	15,566	0.40	6,226	11,282		1.47	22,882	41,462	39,665
	5	17,135	33,110	15,864	2.64	41,881	75,868		0.25	3,966	7,186	
	6	17,142	32,641	15,292	2.94	44,958	81,465		0.29	4,435	8,036	
	7	16,969	32,204	15,129	2.29	34,646	62,778		0.24	3,631	6,578	7,611
	8	17,270	32,835	15,457	2.29	35,396	64,138		0.23	3,555	6,442	6,511
33	1	17,054	33,241	16,074	0.34	5,465	9,903		1.15	18,486	33,496	
	2	17,030	32,751	15,612	0.35	5,464	9,901		1.21	18,890	34,229	33,863
	3	17,021	32,720	15,590	0.45	7,015	12,712		1.35	21,046	38,136	
	4	17,801	32,962	15,552	0.42	6,532	11,836		1.43	22,240	40,298	39,217
	5	17,077	33,057	15,869	2.48	39,355	71,311		0.22	3,491	6,326	
	6	17,112	32,537	15,318	2.75	42,124	76,328		0.24	3,676	6,661	6,494
	7	17,086	32,346	15,154	2.80	42,431	76,885		0.30	4,546	8,238	
	8	16,981	32,553	15,464	2.10	32,474	58,843		0.20	3,093	5,604	6,921
36	1	17,130	33,348	16,105	0.28	4,509	8,171		0.84	13,528	24,513	
	2	17,098	32,821	15,614	0.31	4,840	8,771		1.10	17,175	31,121	27,817
	3	17,133	32,846	15,604	0.45	7,022	12,723		1.28	19,973	36,191	
	4	17,012	32,699	15,578	0.40	6,231	11,291		1.40	21,809	39,518	37,854
	5	17,064	33,035	15,870	2.22	35,231	63,839		0.20	3,174	5,751	
	6	17,215	32,615	15,293	2.68	40,985	74,285		0.23	3,517	6,373	6,062
	7	17,092	32,366	15,168	2.31	36,038	63,488		0.24	3,640	6,596	
	8	17,107	32,684	15,469	2.38	36,816	66,710		0.24	3,712	6,727	6,662
39	1	17,130	33,310	16,068	0.40	6,427	11,646		1.11	17,835	32,317	
	2	16,884	32,598	15,605	0.41	6,398	11,593		1.26	19,662	35,628	33,972
	3	17,161	32,854	15,584	0.51	7,948	14,401		1.32	20,571	37,274	
	4	17,071	32,719	15,539	0.35	5,439	9,855		1.01	15,695	28,439	32,856
	5	16,759	32,714	15,844	1.67	26,460	47,945		0.18	2,862	5,168	
	6	16,921	32,321	15,293	1.61	24,622	44,614		0.15	2,294	4,157	4,662
	7	16,956	32,213	15,152	1.95	29,546	53,538		0.19	2,878	5,217	
	8	16,588	32,162	15,466	2.08	32,169	58,290		0.20	3,093	5,605	5,411
42	1	16,921	33,119	16,085	0.42	6,756	12,242		1.11	17,855	32,353	
	2	17,110	32,811	15,592	0.43	6,704	12,149		1.26	19,546	35,598	33,975
	3	17,076	32,772	15,588	0.55	8,573	15,535		1.31	20,420	37,001	
	4	17,028	32,686	15,551	0.49	7,620	13,808		1.39	21,616	39,168	38,085
	5	17,059	33,046	15,766	2.05	32,546	58,973		0.18	2,858	5,178	
	6	17,077	32,484	15,300	2.40	36,720	66,536		0.20	3,060	5,545	5,361
	7	16,830	32,089	15,153	1.96	29,700	53,816		0.19	2,879	5,217	
	8	17,124	32,680	15,448	1.93	29,814	54,024		0.19	2,935	5,318	5,268

45	1	17,231	33,423	16,079	0.58	9,326	16,899	16,079	1.46	23,476	42,538	42,180
	2	17,185	32,892	15,595	0.54	8,421	15,259	14,822	1.48	23,080	41,822	
	3	17,012	32,710	15,589	0.78	12,159	22,033	18,062	1.79	27,904	50,562	
	4	16,846	32,508	15,553	0.50	7,777	14,091	18,062	1.37	21,308	38,610	44,586
	5	17,229	33,189	15,848	1.64	25,992	47,098	63,250	0.15	2,377	4,308	
	6	17,043	32,472	15,322	2.86	43,820	79,402	51,862	0.26	3,984	7,218	5,763
	7	16,917	32,174	15,151	1.86	28,181	51,064	51,862	0.19	2,879	5,216	5,269
	8	16,937	32,504	15,459	1.88	29,063	52,661	51,862	0.19	2,937	5,322	
48	1	17,121	33,287	16,054	0.56	8,980	16,290	15,068	1.33	21,351	38,689	
	2	17,033	32,737	15,595	0.49	7,641	13,846	15,068	1.28	19,961	36,170	37,429
	3	13,258	28,951	15,584	0.83	9,818	17,790	16,356	1.32	20,571	37,274	
	4	17,334	32,980	15,537	0.53	8,235	14,921	16,356	1.35	20,975	38,007	37,641
	5	16,992	32,943	15,840	1.89	29,938	54,247	57,451	0.18	2,851	5,166	
	6	17,235	32,627	15,285	2.19	33,474	60,655	53,587	0.21	2,904	5,262	5,214
	7	17,271	32,491	15,114	1.99	30,077	54,500	53,587	0.19	2,936	5,319	5,535
	8	17,118	32,677	15,451	1.88	29,048	52,634	53,587	0.19	2,936	5,319	
51	1	16,971	32,878	15,786	0.62	9,794	17,748	15,258	1.49	23,537	42,648	
	2	17,206	32,633	15,320	0.46	7,047	12,769	15,258	1.22	18,690	33,866	38,257
	3	16,917	32,348	15,324	0.65	9,960	18,048	15,815	1.36	20,840	37,763	
	4	16,955	32,359	15,297	0.49	7,495	13,582	15,815	1.30	19,886	36,033	36,898
	5	16,657	32,339	15,573	1.68	25,851	46,842	50,542	0.26	4,049	7,337	
	6	16,943	32,091	15,043	1.99	29,935	54,242	50,542	0.30	4,513	8,177	7,757
	7	16,703	31,683	14,876	1.74	25,884	46,902	45,468	0.29	4,314	7,817	
	8	16,994	32,289	15,189	1.60	24,302	44,035	45,468	0.25	3,797	6,880	7,349
54	1	17,029	32,929	15,789	0.65	10,263	18,597	15,823	1.48	23,368	42,344	
	2	16,939	32,369	15,323	0.47	7,202	13,049	15,823	1.19	18,234	33,040	37,692
	3	17,242	32,676	15,327	0.71	10,882	19,718	20,089	1.36	21,151	38,325	
	4	14,706	30,071	15,258	0.74	11,291	20,459	20,089	1.87	28,533	51,701	45,013
	5	16,986	32,659	15,564	1.95	30,350	54,994	53,683	0.00	0,000	0,000	
	6	17,066	32,231	15,060	1.92	28,914	52,393	53,683	0.28	4,217	7,641	3,820
	7	17,187	32,196	14,905	1.55	23,102	41,861	42,708	0.26	3,875	7,022	
	8	17,233	32,553	15,214	1.58	24,037	43,556	42,708	0.25	3,803	6,892	6,957
57	1	16,902	32,815	15,802	0.51	8,059	14,603	13,419	1.16	18,331	33,215	
	2	17,234	32,686	15,345	0.44	6,752	12,234	13,419	1.11	17,032	30,863	32,039
	3	17,151	32,599	15,341	0.71	10,892	19,736	16,668	1.37	21,017	38,082	
	4	16,850	32,251	15,294	0.49	7,494	13,579	16,668	1.24	18,964	34,364	36,223
	5	16,890	32,590	15,591	1.99	31,026	56,219	44,761	0.37	5,769	10,453	
	6	16,504	31,674	15,085	1.22	18,379	33,302	44,761	0.21	3,164	5,732	8,093
	7	17,102	32,116	14,910	0.99	14,761	26,746	22,994	0.19	2,833	5,133	
	8	16,743	32,020	15,171	0.70	10,620	19,243	22,994	0.13	1,972	3,574	4,353

60	1	16,951	32,870	15,808	0,27	4,268	7,734	7,062	0,58	9,169	16,614	15,808
	2	17,105	32,547	15,335	0,23	3,527	6,391		0,54	8,281	15,005	
	3	17,155	32,622	15,359	0,32	4,915	8,906		0,57	8,755	15,864	
	4	17,103	32,519	15,309	0,25	3,827	6,935	7,920	0,61	9,398	16,921	16,383
	5	17,084	32,787	15,594	0,68	10,604	19,214		0,12	1,871	3,391	
	6	17,049	32,196	15,042	0,83	12,485	22,622	20,918	0,14	2,106	3,816	3,603
	7	16,983	32,005	14,908	0,68	10,137	18,369		0,13	1,938	3,512	
	8	17,108	32,415	15,201	0,67	10,184	18,454	18,411	0,13	1,976	3,581	3,546
63	1	17,163	33,081	15,807	0,28	4,426	8,020		0,57	9,010	16,326	
	2	17,025	32,478	15,346	0,23	3,529	6,395	7,208	0,53	8,133	14,737	15,532
	3	17,136	32,563	15,320	0,32	4,902	8,883		0,56	8,579	15,545	
	4	17,104	32,511	15,300	0,25	3,825	6,931	7,907	0,58	8,874	16,080	15,812
	5	16,849	32,534	15,578	0,66	10,280	18,628		0,12	1,869	3,387	
	6	16,974	32,129	15,050	0,81	12,190	22,089	20,358	0,14	2,107	3,818	3,602
	7	16,555	1,572	14,905	0,66	9,898	17,826		0,13	1,938	3,511	
	8	17,163	32,473	15,204	0,66	9,882	17,907	17,868	0,12	1,824	3,306	3,408
66	1	17,088	32,994	15,795	0,39	6,160	11,162		0,77	12,162	22,038	
	2	16,922	32,375	15,346	0,25	3,836	6,952	9,057	0,55	8,440	15,293	18,686
	3	17,115	32,562	15,340	0,33	5,062	9,172		0,53	8,130	14,732	
	4	16,603	32,021	15,311	0,39	5,971	10,820	9,996	1,03	15,770	28,576	21,654
	5	17,196	32,888	15,583	1,29	20,102	36,425		0,23	3,584	6,494	
	6	17,124	32,253	15,024	1,57	23,587	42,740	39,563	0,27	4,056	7,350	6,922
	7	16,883	31,869	14,882	1,23	18,305	33,168		0,24	3,572	6,472	
	8	17,174	32,489	15,209	1,23	18,707	33,896	33,532	0,23	3,498	6,338	6,405
69	1	16,919	32,835	15,805	0,55	8,693	15,752		1,04	16,438	29,785	
	2	17,089	32,527	15,331	0,47	7,205	13,056	14,404	1,01	15,484	28,057	28,921
	3	17,259	32,729	15,362	0,73	11,215	20,321		1,16	17,820	32,291	
	4	16,857	32,264	15,300	0,50	7,650	13,862	17,091	1,11	16,983	30,773	31,592
	5	17,196	32,863	15,558	1,26	19,803	35,521		0,23	3,578	6,484	
	6	17,075	32,272	15,091	1,48	22,335	40,471	37,996	0,28	3,924	7,110	6,797
	7	17,161	32,188	14,923	1,35	20,145	36,504		0,26	3,880	7,030	
	8	17,244	32,554	15,204	1,18	17,940	32,508	34,508	0,22	3,345	6,061	6,546
72	1	16,950	32,857	15,796	0,60	9,478	17,174		1,10	17,376	31,485	
	2	16,787	32,230	15,336	0,47	7,208	13,060	15,117	0,99	15,182	27,510	29,498
	3	17,186	32,629	15,336	0,66	10,122	18,340		1,00	16,336	27,788	
	4	17,196	32,621	15,318	0,48	7,353	13,323	15,831	1,06	16,237	29,421	28,605
	5	17,192	32,892	15,591	1,18	18,397	33,336		0,21	3,274	5,983	
	6	17,092	32,273	15,075	1,39	20,955	37,970	35,653	0,24	3,618	6,556	6,244
	7	17,168	32,186	14,914	1,18	17,598	31,888		0,22	3,281	5,945	
	8	16,958	32,256	15,192	1,14	17,318	31,381	31,634	0,21	3,190	5,781	5,863